OSTEOSCOOP

News on current events in osteoporosis and rheumatology

Osteoclast size is controlled by adequate sensitivity to oxygen

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Osteoclasts are cells of a hematopoetic lineage that resorb bone, and excessive activity of these cells can lead to low bone mass with an associated increased incidence of fractures. Osteoclast differentiation requires the transcription factor AP-1, which is a heterodimer of a Jun family member and a Fos family member.

Bozec et al. [1] found that mice deficient for a Fos family member, Fra-2, exhibited increased osteoclast size (giant osteoclasts), number, and activity. The expression and abundance of the leukemia inhibitory factor (LIF) receptor (LIFR) were also decreased in the bones of mice lacking Fra-2. In vitro experiments showed that LIF was a direct target of Fra-2 and Jun. Although no bone phenotype was reported for LIF knockout mice, these mice had osteoclasts that were larger and more numerous with increased resorptive activity, which led to decreased bone volume. Fetal liver-derived osteoclast progenitor cells deficient in either Fra-2 or LIF did not differentiate in culture and exhibited increased apoptosis compared with wild-type cells; however, differentiation into osteoclasts was rescued by the addition of LIF. In vivo, osteoclasts were hypoxic, suggesting that hypoxia may contribute to the giant osteoclast phenotype. Indeed, Fra-2- or LIF-deficient osteoclast progenitors exhibited increased cell death at 21% oxygen, but less cell death at 3% oxygen. Thus, the loss of LIF signaling appears to alter the sensitivity of the cells to oxygen. It appeared that the Fra-2 knockout mice had impaired placental function, because LIF and its receptor were decreased in the placenta.

Thus, proper bone oxygenation in utero requires a functional LIF signaling axis that required Fra-2, and a similar pathway in the bone progenitors was required for proper oxygen responsiveness.

1. Bozec A et al. *Nature*. 2008;454:221-225.

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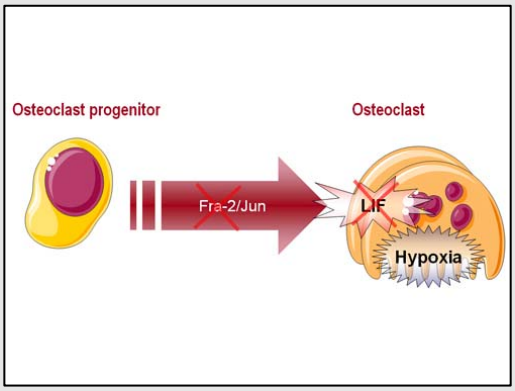

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